REMARKS

Claim Amendments

Claims 29-33, 37-40, 42-44, 46-48, 50-70 are currently pending in the application. Claims 29-33 and claims 53-61 have been withdrawn by the Examiner as being drawn to a non-elected invention. Claims 3, 6, 9, 12, 34-36, 41, 45 and 49 have been newly cancelled without prejudice, with the limitation of claim 34 having been incorporated into currently amended claims 37, 38, 42, 46 and 50. Claims 29-33, 37-40, 42-44, 46-48 and 50 are newly amended. Claims 62-70 are newly added, with claims 63 and 64 reciting the subject matter of newly cancelled claims 35 and 36, respectively. Support for claims amendments is found throughout the specification and in the originally filed claims and are discussed in the relevant sections below. No new matter is added.

Independent claim 37 has been amended so as to more clearly indicate that the claim recites comparing levels of TNFAIP6-encoded RNA in a sample of a test individual with levels of TNFAIP6-encoded RNA in samples of control individuals, and comparing levels of TGFBI-encoded RNA in a sample of a test individual with levels of TGFBI-encoded RNA in samples of control individuals. Support for such comparison between expression levels of the same gene in different samples is provided in the published application US20040209275 (referred to herein as "the published application", unless indicated otherwise), for example, at paragraph [0125], paragraph [0169], 1st sentence, and throughout the examples section. Support for the recitation of a "set" of genes is provided, for example, at paragraph [0112] of the published application. The Examiner will note that Applicant has corrected a typographical error in the spelling of the gene symbol for specification transformation growth factor, beta-induced, 68kDa from TGFB1 to TGFBI. Support for this amendment can be found in Table 6b, lines 18 and 19 p.61 and 62 and Table 7a line 1120 p 753, all of which cite the gene as "transforming growth factor, beta induced, 68kDa (TGFBI)" with a reference accession number of NM_000358". Applicant would note that TGFB1 (transforming growth factor beta 1) reference accession number NM_000660 is not disclosed anywhere in the specificationi. Should this typographical error raise unforseen concerns, Applicant would request a telephone conference with the Examiner to discuss further.

Claims 37, 38, 42, 46 and 50 have been amended so as to limit the recited samples to those which are samples of cartilage. Support for limiting the samples to cartilage is found

throughout the specification, for example, at Examples 1-6, and at paragraph [0121].

Independent claims 37, 38, 42, 46 and 50 have been amended so as to limit the invention to a method of diagnosing a stage of osteoarthritis in a human test individual by comparison to human control individuals. Support for reciting diagnosis of a stage of OA in a human individual by comparison to human control individuals is clearly consistent with the teachings throughout the specification, including at original claim 34, and paragraphs [0226] and [0275] of the published application.

Independent claims 38, 42, 46 and 50 have been amended, to incorporate the limitation of now canceled claim 34 that the sample is human cartilage, and also to clarify that the method of diagnosing of a stage of osteoarthritis requires (a) **determining** the level of RNA encoded by **each** recited gene in a cartilage sample of a human test individual, and (b) **comparing** said level with the level of expression of RNA encoded by **each** gene in control cartilage samples from five populations of human individuals (i) individuals not having osteoarthritis; (ii) individuals having mild osteoarthritis according to the Marshall scoring system (iii) individuals having moderate osteoarthritis according to the Marshall scoring system (iv) individuals having marked osteoarthritis according to the Marshall scoring system and (v) individuals having severe osteoarthritis according to the Marshall scoring system and (c) **determining a difference** in the levels of expression as between RNA encoded by said genes in the test individual and the same genes in the control populations such that the test individual is classified as having a particular stage of osteoarthritis.

Support for this amendment can be found throughout the specification including at paragraph [0138], Example 5 at paragraph [0449], Example 6 at paragraph [0453] of the published application. As described therein, where a difference is determined in the level of expression when comparing the normal population and the disease population using known statistical methods, one can determine whether a test individual is correctly classified as between the two populations. The extension of this same methodology to comparisons with other stage specific populations is clearly contemplated, for example, in Example 5 at paragraph [0449] .

Claims 39, 43, 47 and 51 have been amended so as to reflect the amended language of claims 38, 42, 46 and 50 from which they depend, respectively.

Claims 40, 44, 48 and 52 have been amended so as to reflect the amended language of claims 38, 42, 46 and 50 from which they depend, respectively.

Claim 62 has been newly added limiting claims 37, 38, 42, 46 and 50 so as to recite that "a cDNA or EST complementary to said RNA encoded by said gene is immobilized to a microarray". Support for this limitation can be found, for example, at paragraphs [0109] and [0217] of the published application.

Claims 65 and 66 have been newly added limiting the gene of claim 38 to one identified in Figure 6a or 7a, respectively. Claims 67 and 68 have been newly added limiting the gene of claim 42 to one identified in Figure 6d or 7b, respectively. Claim 69 has been newly added limiting the gene of claim 46 to one identified in Figure 6b, and claim 70 has been newly added limiting the gene of claim 50 to one identified in Figure 6c. Specification support for these amendments can be found in Example 6 of the published application.

Specification

The Examiner suggests that figures containing text concerning differential expression of genes in OA be incorporated as TABLES into the specification so as to make the information more search-accessible to the public in the event this application issues as a patent.

The Examiner requests identification and deletion from the disclosure of all embedded hyperlinks (e.g. page 59, line 9 and page 93, line 17) and/or other form of browser-executable code.

The Examiner requests appropriate correction of the misspelled word "from" at page 97, line 16 of the disclosure.

Applicant will consider incorporating as TABLES into the specification text concerning differential expression of genes in OA, upon the indication of allowable claims.

In accordance with the Examiner's requests, Applicant has, above, identified and deleted from the specification embedded hyperlinks, and has corrected the misspelled word "from" at page 97 of the disclosure.

Claim Objections

The Examiner objects to claims 34-36 on the grounds that these depend from claims withdrawn as being drawn to a non-elected invention.

Applicant has cancelled claims 34-36 without prejudice to Applicant's rights to pursue related claims and has added new claim 63 and 64 which essentially recite the limitations of

claims 35 and 36, respectively, and which depend only from claims drawn to an elected invention. The limitation of claim 34 has been added to claims 37, 38, 42, 46 and 50.

In view of this amendment, Applicant respectfully requests reconsideration and withdrawal of the objection.

Double Patenting

The Examiner states that claims 35, 36, 38, 42, 46 and 50 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13, 21 and 25 of copending Application No. 10/809, 675 (referred to herein as "the '675 application").

While respectfully disagreeing with the contention that the claims, including new claims 63 and 64 essentially reciting the limitations of cancelled claims 35 or 36, respectively, can be rejected under double patenting rejections, Applicant will consider filing a terminal disclaimer should it be necessary upon the indication of allowable claims.

35 U.S.C. § 112 Rejections

Indefiniteness

The Examiner has rejected claims 34-52 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Specifically, the Examiner contends that independent claims 37-38, 41-42, 45-46 and 49-50, and dependent claims thereof, are vague and indefinite on the grounds that the metes and bounds of the phrase "RNA corresponding to" are unclear. The Examiner informs Applicant that it would be remedial to amend the claim language to clearly indicate what RNA is being measured in the claimed methods.

Applicant respectfully disagrees with the contention that claims 34-52, and claims depending therefrom, are indefinite, on the grounds that the metes and bounds of the phrase "RNA corresponding to" is unclear. Nevertheless, in the interest of expediting prosecution of the application, but without prejudice to Applicant's rights to pursue related claims, Applicant has amended this language in claims 37-38, 42, 46 and 50 so as to replace the recitation "*RNA corresponding to*" with the recitation "*RNA encoded by*" to more clearly indicate the RNA being

referred to in the claims is RNA which is encoded by the gene in said sample. Specification support for the recitation "*RNA encoded by*" can be found, for example, at paragraph [085], [086] and paragraph [0261] of the published application.

The Examiner also contends that dependent claims 39, 43, 47 and 51 are vague and indefinite on the grounds that the metes and bounds of the phrase "one or more biomarkers are selected from those identified in Figures 1-7" is unclear. Applicant has amended claims 38, 42, 46 and 50 from which the objected to claims depend, to clarify that comparison is to be done for each gene of a set of genes. In claims 39, 43, 47 and 51, Applicant has amended these claims to clarify that each gene is to be one identified in Figures 1-7. Applicant respectfully submits that Tables 1-7 clearly identify the claimed genes according to various identifiers including the description of the gene itself, the NCBI reference accession number, the unigene cluster and the NCBI protein accession number. These descriptors were well understood by the ordinarily skilled artisan to identify the genes being referred to, and therefore clearly identify the RNAs which are encoded by the gene and which are to be detected and compared. In view of the latter amendment Applicant believes to have adequately addressed the issue raised by the Examiner concerning the clarity of the metes and bounds of the phrase "one or more biomarkers are selected from those identified in Figures 1-7" and which are encompassed by currently amended claims 38, 42, 46 and 50.

In view of the claim amendments, and Applicant's arguments, reconsideration and withdrawal of the rejection is respectfully requested.

Enablement

Claims 34-52 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicant respectfully traverses the rejection that in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention.

As disclosed in the specification, osteoarthritis, especially mild osteoarthritis, is currently very difficult to diagnose. The physician relies primarily on the patient's history and physical exam to make the diagnosis of osteoarthritis and X-rays do not show the underlying early

changes in articular cartilage. At the time of the invention, there were no recognized biochemical markers used to detect mild osteoarthritis. Symptoms, such as episodic joint pain, are a common manifestation of early osteoarthritis. Joints become tender during an episode, which can last days to weeks and remit spontaneously. These symptoms however, often do not correlate well with the pathological stages of damage to the cartilage. A more reliable method of detecting "mild" osteoarthritis can be obtained by determining the extent of cartilage damage, however there is currently no method for measuring cartilage deterioration which is relatively non-invasive. Applicant has provided a simple non-invasive diagnostic test for detecting various stages of osteoarthritis, including mild osteoarthritis, which uses differential gene expression as indicated by the instant claims.

The instantly filed independent claims are currently amended claims 37, 38, 42, 46 and 50. Currently amended claim 37 is solely drawn to diagnosis of the presence of **at least mild OA** by comparison of expression levels in cartilage of RNA encoded by a gene, for each of the genes TNFAIP6 and TGFBI, as between a test individual and normal control individuals not having osteoarthritis. Currently amended claims 38, 42, 46 and 50 are drawn to the diagnosis of either mild, severe, moderate or marked OA, respectively, by comparison of expression levels of RNA encoded by a gene, for each gene of a set of genes, between a test subject and control samples comprised of populations of individuals not having osteoarthritis and populations of individuals having osteoarthritis, for each of the four stages of osteoarthritis in accordance with the Marshall scoring system. Applicant's remarks concerning claim 37, and concerning claims 38, 42, 46 and 50 are separately set forth below.

Enablement of Claim 37

Breadth of the Claims

Issues of concern were raised by the Examiner relating to enablement of the full breadth of the claims, namely with respect to the use of any sample type (e.g. blood, synovial fluid, cartilage) from any species of organism, so as to include the diagnosis of OA in any species. In the interest of expediting prosecution, and without prejudice to the Applicant's rights to pursue the subject matter of the unamended claims in other applications, claim 37 has been amended so as to limit the recited samples to **cartilage** samples, and has further amended the claim so as to

be drawn simply to the diagnosis of mild OA in a **human** individual. Since currently amended claim 37 recites samples which are limited to cartilage samples, and the claim is drawn to diagnosis of a test individual limited to a human, Applicant believes to have adequately addressed the Examiner's concerns in this regard.

The Examiner also appears concerned that the language used to define the detected RNA is broad enough to encompass RNA expressed "from genes that are homologs, variants and the like". As discussed above, Applicant has amended the language so as to specify that the RNA referred to is (i) RNA encoded by the gene of interest and (ii) RNA encoded by that gene which is detected in a cartilage sample. The measurement of RNA in the sample would therefore be expected to include only RNA transcripts which are encoded by the gene and expressed in the cartilage sample. While the RNA detected may therefore include variants, it would be understood by a skilled artisan that homologs of the gene of interest are NOT included.

Guidance of the Specification and Existence of Working Examples

The Examiner appears concerned that the specification fails to provide sufficient guidance to a person skilled in the art as to the practicing of the invention in Claim 37. In particular the Examiner cites the lack of a working example for the diagnosing of OA or a stage of OA.

Reduction to practice of the invention prior to filing is not required (Gould v. Quigg, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987)). "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting In re Chilowsky, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)).

Applicant has amended current claim 37 to focus on the use of the gene expression pattern of TNFAIP6 and TGFBI for the specific purposes of diagnosing an individual of having at least **mild OA**, without prejudice to the Applicant's rights to claim the subject matter of the cancelled claims at a later date. As currently amended, claim 37 requires comparing the level of expression of both TNFAIP6 **and** TGFBI to the level of expression of RNA encoded by said gene in control samples so as to be indicative of mild osteoarthritis. As noted by the Examiner,

the specification must therefore teach a person skilled in the art to utilize the genes TNFAIP6 and TGFBI to detect the presence of mild osteoarthritis in a test individual.

The specification clearly contemplates and teaches methods to identify genes which are indicative of a stage of disease such that the pattern of expression is found significantly more often in patients with a stage of disease as compared with patients without the disease (see paragraph [0143]). The specification also teaches identifying differences in the level of expression which can differentiate as between a stage of disease and a population which is comprised of control individuals not having osteoarthritis (see paragraph [0139]). The use of these genes for diagnostic purposes are described in paragraphs [0395] – [0397] which dictate "a sample comprising nucleic acid corresponding to RNA is prepared from the patient cartilage sample ... and hybridized to an array ...where at least one member is differentially expressed in cartilage isolated from a patient diagnosed with mild ...osteoarthritis as compared to a "normal individual", ...[where] [a]ccording to this diagnostic test, differential hybridization of RNA of the sample as compared to a normal control is indicative of disease". Figure 7 describes genes which were identified as described in Example 6 as differentially expressed when comparing mild OA to normal. With respect to the genes TNFAIP6 and TGFBI,

(i) TNFAIP6 and TGFBI are both differentially expressed in individuals having mild OA (Figure 7a, line 921 and 1120 of Affymetrix U133A array data, as clearly confirmed in the enclosed Declaration under 37 C.F.R. § 1.132 (referred to as "the Declaration" unless indicated otherwise).

(ii) Neither TNFAIP6 nor TGFBI are differentially expressed in individuals having severe OA (see Figure 7)

Applicant notes that the data disclosed in Figure 7(a), as confirmed by the declaration, demonstrates that, as compared to individuals diagnosed as not having OA, <u>both</u> TNFAIP6 and TGFBI are differentially expressed in individuals having mild OA. While Figure 7(b) also demonstrates that TNFAIP6 and TGFBI are NOT both differentially expressed in individuals having severe OA, the Applicant would note that a person skilled in the art would understand that this is not necessary, in accordance with the teachings of the specification and the claims, for TNFAIP6 and TGFBI to be considered indicative of at least mild OA, so long as the claim does not require that the genes be indicative of **only** mild OA. Therefore the gene expression pattern

for these two genes is one which is indicative of mild OA. These results are described in Figure 7 and can be readily determined by the ordinarily skilled artisan from the following specification teachings regarding differential gene expression in individuals diagnosed with a stage of OA relative to normal controls.

The Examiner correctly notes that TGFBI is found in Figure 6b as a gene which is specific to moderate OA only and TNFAIP6 is found in Figure 6c as found in marked OA. As would be understood by a person skilled in the art, this is not inconsistent with the current claims which require that both genes be differentially expressed so as to be indicative of mild osteoarthritis.

The Examiner also notes that the specification does not teach the direction of expression for those genes noted in Figures 6 and 7. Applicant respectfully submits that currently amended claim 37 is well within the means of the person skilled in the art to practice without foreknowledge of the directionality of expression of the genes noted since the direction of differential expression is an inherent feature of the TNFAIP6 and TGFBI genes in mild OA cartilage as compared with cartilage samples from normal individuals. It is well understood that even a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In this case the experimenttion required to determine directionality is routine and well within the guidance of the specification. Thus, the Applicant respectfully disagrees that it is required for the specification to teach the direction of expression of TNFAIP6 and TGFBI in order to practice the claimed invention successfully.

Predictability and State of the Art

The Examiner raises a number of concerns regarding the predictability of the state of the art. More specifically the Examiner appears concerned that the person skilled in the art would not be able to practice the claimed invention and in this regard notes some post filing references to suggest that the state of the art is unpredictable with regards to practicing the claimed method.

With respect to the Examiner's remarks that Shalon *et al.* teaches that samples from at least 5 different test individuals are assayed to reliably identify differentially expressed genes, Applicant wishes to point out that Shalon *et al.* in fact recites at paragraph [0155] that "*Typically,*

samples from at least 5... test individuals are assayed to obtain statistically meaningful data..." Applicant notes that Shalon *et al.* clearly does not exclude use of samples from fewer than 5 test individuals to identify differentially expressed genes, and clearly recognizes that five or more is sufficient.

As described in the accompanying Declaration, for the most part, the experiments described in Example 6 resulting in the genes noted in Figures 6 and 7, utilized more than 5 test individuals although in some cases the number of samples used were slightly less than five. Experiments performed using the ChondroChip platform, for example, were performed with 6 normal samples, 3 mild OA samples, 8 moderate OA samples, 7 marked and 13 severe OA samples. Similarly experiments described in Example 6 utilizing the Affymetrix platform used 10 normal, 4 mild OA samples and 5 severe OA samples.

The accompanying Declaration provides further data obtained from 10 individuals not having osteoarthritis and 20 individuals diagnosed as having mild osteoarthritis and continues to demonstrate that the gene expression of both TNFAIP6 and TGFBI is differentially expressed in cartilage of individuals having mild OA relative to individuals not having OA resulting in a diagnosis of mild OA with a sensitivity of 90% and a specificity of 70%.

With regard to the Examiner's comments whereby Shalon et al teach biomarkers typically exhibiting a differential expression of at least 2 fold, although Applicant does not necessarily agree that this is a requirement, the Applicant notes that the Declaration clearly demonstrates that both TNFAIP6 and TGFBI demonstrate a differential expression of more than two-fold in individuals diagnosed with mild OA as compared to normal control individuals, in accordance with the preferred embodiment of the invention taught by Shalon *et al.* which was cited by the Examiner.

With regard to the Examiner's comments whereby post-filing art Kroese *et al.* and Lucentini teach the state of the art has significant limitations in relation to the predictability of the claimed invention, Applicant wishes to respectfully point out that both of these references relate only to use of genetic testing for diagnosis of genetic conditions which are based on DNA sequence differences between normal individuals and individuals. This is clearly evident throughout Kroese *et al.* and, e.g. at page 475, column 2, complete paragraph which introduces the scope of the teachings of Kroese *et al.* as such according to the following recitation: "*For our purposes we focus on the concept of a gene test, defining that one based on the analysis of*

human DNA using a variety of gene tests. In this review, any reference to a genetic test will be taken to refer to a gene test." Lucentini as well clearly relates to correlation of diseases with only genetic (DNA) sequences *per se*, as evidenced, for example, by the title, by reference to studies associating schizophrenia with dopamine D3 receptor mutations (p. 2, 1st paragraph) and throughout the text in general. Applicant respectfully submits that the cited teachings of Kroese *et al.* and Lucentini are therefore not applicable to the claimed invention which claims disease diagnosis methods which are based on determination of differential expression/RNA levels of genes such as wild-type genes, and which are thereby clearly distinct from methods only based on analysis of DNA sequences.

In relation to the Examiner's remarks to the effect that Marshall *et al.* teaches that extensive statistical analysis of numerous training and test samples must be done to determine the specificity, sensitivity and accuracy of an OA diagnostic test based upon gene expression assays, Applicant would refer to the attached Declaration which demonstrates similar statistical analysis demonstrating the utility of the currently selected genes.

Claims 38, 42, 46 and 50

The Examiner has raised concerns as to the enablement of the full breadth of the claims, namely with respect to the use of any sample type (e.g. blood, synovium, cartilage) from any species of organism, so as to include the diagnosis of OA in any species. The Examiner further contends that:

> "one would have required a large amount of experimentation to carry out the claimed invention",
>
> and
>
> "the practice of the invention for the diagnosis of osteoarthritis requires the knowledge of gene(s) that are differentially expressed between normal, mild osteoarthritis, moderate osteoarthritis, marked osteoarthritis and severe osteoarthritis...In other words the gene expression patterns tested in the claimed methods must allow one to draw a reliable conclusion regarding the presence/absence of osteoarthritis and the severity of osteoarthritis".

Applicant respectfully disagrees that a large amount of experimentation is required to carry out the claimed invention and further submits that Applicant has provided specific guidance with respect to methods concerning how to diagnose osteoarthritis using differential

gene expression, as evidenced by the prolific data detailed in the Tables and Figures of the specification.

Solely in order to expedite prosecution and without prejudice to pursuit of subject matter of the current claims, Applicant has amended the claims so as to limit the scope of the claims to deal with diagnosis of osteoarthritis using **cartilage** samples from **human** individuals.

Applicant submits that these amendments significantly narrows the current claims. The Applicant further notes that a broad claim does not need be exemplified by a large number of examples of operativity of the claimed invention. Were this the case, then no broad claim would ever be allowed and the legal concept of constructive reduction to practice would not exist. It is further submitted that claims are not broader than the enabling disclosure if "a person skilled in the relevant art could determine which conceived but not-yet-fabricated embodiments would be inoperative with expenditure of no more effort than is normally required" in the art. (169 USPQ at 302.) Because of the availability and use of techniques to analyze differential gene expression at the time the instant invention was made, (such as microarray and real time quantitative RT-PCR), Applicant submits that a person skilled in the relevant art at the time the invention was made, could readily determine which genes of those detailed in the disclosed tables and figures, would be operative within the scope of the invention, as discussed supra, since the means of detecting differential gene expression, as well as the means of correlating differential gene expression patterns with disease in a statistically significant manner, were both routine to one of skill in the art at the time the invention was made. Specific support for the current invention can also be found at paragraph [0139], Example 5 at paragraph [0449], Example 6 at paragraph [0453] of the published application.

Hence, Applicant submits that the instant disclosure satisfies the enablement requirement of 35. U.S.C. 112, first paragraph.

Applicant contends that the disclosed tables and figures provide genes which are differentially expressed in various stages of ostearthritis, and which form gene expression patterns which can be reliably correlated to a the presence/absence/severity of ostearthritis. In establishing this nexus, Applicant has designed a system of scoring the presence and/or severity of osteoarthritis whereby subjective decisions by the arthroscopist are minimized. As disclosed in the instant specification:

> "The scoring system which defines disease states described herein is that of Marshall, supra, incorporated herein by reference. According to this method, each of the 6 articular surfaces (patella, femoral trochlea, medial femoral condyle, medial tibial plateau, lateral femoral condyle and lateral tibial plateau) is assigned a cartilage grade based on the worst lesion present on that specific surface. A scoring system is then applied in which each articular surface receives an osteoarthritis severity number value that reflects the cartilage severity grade for that surface, as described in Table 1."

By correlating this novel and relatively objective system of scoring different stages of osteoarthritis, including the difficult to score stage of mild osteoarthritis, to differential expression levels of the genes identified in the instant tables, Applicant has provided non-invasive methods of diagnosing osteoarthritis, and specific stages thereof, comprising the identification of specific gene expression patterns which correlate to specific stages of osteoarthritis. The office action asserts that "characteristics of a genetic test should be presented with their 95% confidence intervals". Applicant notes that the specifications provides for 95% confidence intervals, as outlined in the following excerpt from the specification:

> "As used herein, "indicative of disease" refers to an expression pattern which is diagnostic of disease or a stage of disease such that the expression pattern is found significantly more often in patients with a disease or a stage of disease than in patients without the disease or another stage of disease **(as determined using routine statistical methods setting confidence levels at a minimum of 95%)**.", emphasis added

The office action also asserts that a genetic test "should identify genes which show significantly, typically at least 2 fold and up to 100 fold more, increase or decrease in gene expression level with respect to control levels for the same gene". Applicant notes that the specification discloses that sample RNA from either normal mild or severe OA cartilage was labeled and hybridized to the Chondrochip with subsequent analysis identifying differences in gene expression **greater than 2-fold** when compared to either the intensity from the normal cartilage or any other stage specific cartilage (page 97), and Figures 1-4 provide those genes identified as unique by this criteria to mild or severe osteoarthritis.

The specification notes that it "would be understood by a person skilled in the art that two or more of these genes, or the products of these genes in combination are useful as biomarkers" for osteoarthritis". Using well-established and accepted analytical tools, Applicant submits that the experimentation required to apply the observation across diseases, while requiring time and effort, is not undue, as evidenced by *In re Wands*.

The essence of the invention of currently amended claims 38, 42, 46 and 50is the utility of samples from individuals which have been categorized as having one of four stages of osteoarthritis in accordance with the Marshall scoring system. Thus, what the Applicant has disclosed and now claims is the usefulness of this categorization system to identify genes which exhibit RNA expression levels in **cartilage** which are unique to one, and which can thereby be used for diagnosis of, one of the four given stages of osteoarthritis.

Finally the Examiner expresses concerns regarding the predictability and state of the art and considers that the amount of experimentation necessary is undue. As noted, "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Applicant has provided sufficient support within the specification to put the method of diagnosing of specific stages of osteoarthritis into the hands of a person skilled in the art. The method disclosed is novel, and clearly has utility which fulfills a longstanding need in the art.

In view of Applicant's arguments, reconsideration and withdrawal of the rejection is respectfully requested.

Conclusion

Applicant submits that all claims are allowable as written and respectfully requests early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney's/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

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Respectfully submitted,

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